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Research Article

DEVELOPMENT AND EVALUATION OF CONTROLLED RELEASE FORMULATIONS OF ESOMEPRAZOLE

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ABSTRACT

The present work was aimed to development of controlled release formulations of Esomeprazole to improve bioavailability. Esomeprazole is the proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. By acting specifically on the proton pump, Esomeprazole blocks the final step in acid production, thus reducing gastric acidity. Construction of calibration curve of Esomeprazole and to investigate the drug and polymer interaction studies by FTIR and DSC. To prepare the different controlled release formulations of Esomeprazole tablets with different polymers like Polymethacrylates such as Eudragit-S100, Eudragit-L100, Eudragit-RSPO, Eudragit-RS100, Eudragit-RL100 and Eudragit RLPO by Direct Compression method. Evaluation of Esomeprazole pre compression parameters such as Bulk density, Tapped density, Hausner's ratio, Carr's index, Angle of repose. Evaluation of post-compression parameters of Esomeprazole controlled release tablets such as Weight variation, Hardness, Friability test, Thickness, Drug Content and *In-vitro* dissolution studies. Evaluation of *in-vitro* dissolution uniqueness of all the formulations of Esomeprazole by using USP dissolution apparatus type-II (paddle). To study the mechanism of drug dissolution by applying kinetic parameters. To perform the stability studies of optimized formulations of Esomeprazole as per ICH guidelines.

INTRODUCTION

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to acquire quick and entire systemic drug absorption. Such immediate release products result in comparatively rapid drug absorption and onset of associated pharmacodynamic effects. Although, after absorption of the drug from the dosage form is whole, plasma drug concentrations refuse according to the drugs PK profile. Ultimately plasma drug concentrations reduce below the minimum effective plasma concentration (MEC), ensuing in loss of therapeutic activity. Before this point is reached, another dose is frequently given if a sustained therapeutic effect is required. A substitute to administer an additional dose is to use a dosage form that will afford sustained drug release, and hence maintain plasma drug concentrations, ahead of what is typically seen using immediate release dosage forms.

MATERIALS AND METHODS

Esomeprazole is highly effective inhibitor of gastric acid secretion used in the therapy of stomach ulcers and zollinger-ellison syndrome. The drug inhibits the H(+)-K(+)-ATPase (H(+)-K(+)- exchanging ATPase) in the proton pump of gastric parietal cells.

Structure:

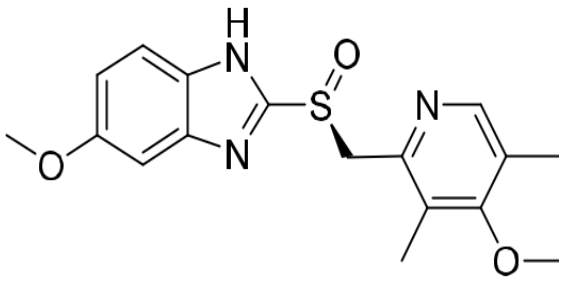

Figure No: 1 Structure of Esomeprazole

***Chemical Formula*:** $C_{17}H_{19}N_3O_3S$

Molecular weight: Average: 345.416, Monoisotopic: 345.114712179 g/mol.

IUPAC Name: 5-methoxy-2-[(S)-(4-methoxy-3,5-dimethylpyridin-2yl)methane sulfinyl]-1H-1,3-benzoimidazole.

Solubility: Soluble in methanol, DMSO (143 mg/ml at 25 °C), ethanol (143 mg/ml at 25°C), and water (<1 mg/ml at 25°C)

Categories: Proton Pump Inhibitors (PPI), Gastroesophageal reflux disease (GERD).

Pharmacokinetic data:

Bio-Availability : 50% - 90%

Protein Binding : 97 %

Metabolism : Hepatic

Excretion : 80% Renal and 20% in the Feces

Half Life : 1 to 1.5hours

Mechanism of Action: Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. By acting specifically on the proton pump, Esomeprazole blocks the final step in acid production, thus reducing gastric acidity.

List of chemicals used in study and their manufacturers is shown in Table 1 and List of equipments used in study and their manufacturers is shown in Table 2.

Table 1: List of chemicals used in study and their manufacturers

S. No	Chemicals	Manufacturer	Purpose
1.	Esomeprazole	Astra Zeneca Pharma Ltd, Bangalore	API
2.	Eudragit-S 100	Evonik Health Care, Germany	Polymer
3.	Eudragit –L 100	Evonik Health Care, Germany	Polymer
4.	Eudragit RSPO	Yarrow Chem. Products, Mumbai	Polymer
5.	Eudragit RS 100	S.D Fine Chem. Ltd, Mumbai	Polymer
6.	Eudragit-L 100	S.D Fine Chem. Ltd, Mumbai	Polymer
7.	Eudragit RLPO	Yarrow Chem. Products, Mumbai	Polymer
8.	Talc	Yarrow Chem. Products, Mumbai	Glidant
9.	Magnesium Stearate	Yarrow Chem. Products, Mumbai	Lubricant
10.	Di calcium phosphate	Akhil Health care Pvt. Ltd, Gujarat	Diluent

Table 2: List of equipments used in study and their manufacturers

S. No	Instruments	Make	Model
1.	Tablet Compression Machine	Karnavathi	Rimek mini press I
2.	FT-IR spectrophotometer	Bruker	Alpha-T-1020
3.	Differential Scanning Calorimetry	Hitachi	6300
4.	HPLC	Agilent Technologies	1200
5.	UV-Visible spectrophotometer	Lab india	UV 3200+
6.	Dissolution test apparatus	Lab india	DS-8000
8.	Electronic Weighing balance	Shimadzu	ATX224
9.	Friabilator	Lab india	FT 1020
10.	Hardness tester	Monsanto	SISCO
11.	Tapped density apparatus	Lab india	TD 1025
12.	Bulk density apparatus	Thermonik	PD-100
13.	Sonicator	Ultrasonic's,	1.5L (H)
14.	Centrifuge	Remi	C-854/6
15.	Hot air oven	Universal	D-5247
16.	Seive no's 16,40 and 60	Jayant Scientific	J-82
17.	Stability chamber	Cintex IC	CIC-64 AA
18.	P^H meter	Lab india	SAB 5000

PREFORMULATION STUDIES:

The goals of the preformulation study are:

- ✓ To establish the necessary physicochemical characteristics of a new drug substance.
- ✓ To determine its kinetic release rate profile.
- ✓ To establish its compatibility with different excipients.

Hence, preformulation studies on the obtained sample of drug include colour, taste, solubility analysis, melting point determination and compatibility studies and flow properties.[38, 39]

Preparation of standard solutions of Esomeprazole

Accurately weighted 10mg Esomeprazole (working standard) was transferred into a 10 ml volumetric flask.7ml of diluent was added and sonicated to dissolve the powder drug completely and finally volume was made up to the mark with the same solvent (stock solution). Further 1.0 ml of the above stock solution was pipette into a 10ml volumetric flask and diluted up to the mark with diluent. Finally the preparation was filtered through 0.45µm filter. Different concentrations (1, 10, 20, 30 & 40 µg/ml) were prepared for Linearity test.

Drug and excipient compatibility studies

Determined by using Fourier Transform Infrared Spectroscopy (FTIR) studies and Differential Scaning Caloriemetry (DSC)

Fourier Transform Infrared Spectroscopy (FTIR) studies

The drug- polymer and polymer-polymer interaction was studied by FTIR. Two percent (w/w) of the sample with respect to a potassium bromide disc was mixed with dry KBr. The mixture was ground into a fine powder using an agate mortar and then compressed into a KBr discs in a hydraulic press at a pressure of 10000 psi. Each KBr disc was scanned 16 times at 2 mm/sec at a resolution of 4 cm–1 using cosine apodization. The characteristic peaks were recorded. Ratio of Drug and Excipients taken for compatibility studies is shown in Table 3.

Table 3: Ratio of Drug and Excipients taken for compatibility studies

Ingredients	Ratio of Drug and Excipients
Esomeprazole	1:0
Esomeprazole+Eudragit RSPO	1:1

Differential scanning calorimetry studies

DSC is a thermoanalyticaltechnique in which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the experiment. Generally, the temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. The reference sample should have a well-defined heat capacity over the range of temperatures to be scanned.

Flow properties [41-44]

Angle of Repose

It is performed to determine the flow rate of powder done by the funnel method. The powder was poured into a funnel which is fixed from height of 2cm of the plane surface. Circumference was drawn with a pencil on the graph paper and the radius of base of a pile was measured at 5 different points and average was taken for calculating Angle of repose using following formula:

$\Theta = \tan^{-1} H/R$

Θ=angle of repose,

H=height of powder cone, and

R=radius of powder cone

Angle of Repose less than 300 shows the free flowing property of the material.

Bulk density

Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

Bulk Density = M / Vo

Where, M = weight of sample and

Vo = apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest

graduated unit. The tapped density was calculated, in gm per L, using the formula:

Tap= M / V

Where, Tap= Tapped Density,

M = Weight of sample and

V= Tapped volume of powder

Carr's consolidation index

The Carr index is an indication of the compressibility of a powder.

A Carr index greater than 25 is considered to be an indication of poor flowability, and below 15 of good flowability.

Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material.

Hausner's ratio greater than 1.25 is considered to be an indication of poor flowability.

Formulation Development of Tablets

Preparation of Tablets

Direct Compression method

Different tablets formulations were prepared by direct compression technique. All powders were passed through 60mesh. Required quantities of drug and polymers were mixed thoroughly Magnesium stearate was added as lubricant. Talc was used as glidant. Dicalcium phosphate was used as diluent. Finally the powder mix was subjected to compression after mixing uniformly in a polybag. Prior to compression, the blends were evaluated for several tests.

Esomeprazole Compositions

Table No: 4 Compositions of Esomeprazole CR tablets (F1-F9)

S. No	Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Esomeprazole	20	20	20	20	20	20	20	20	20
2	Eudragit S-100	20	40	---	---	---	---	20	20	---
3	Eudragit L-100	---	---	20	40	---	---	20	---	20
4	Eudragit RSPO	---	---	---	---	20	40	---	---	20
5	Talc	3	3	3	3	3	3	3	3	3
6	Magnesium stearate	3	3	3	3	3	3	3	3	3
7	Di.Calcium Phosphate	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s
	Total Weight	100	100	100	100	100	100	100	100	100

Table No: 5 Compositions of Esomeprazole CR tablets (F10-F19)

S.No	Ingredients (mg/tab)	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19
1	Esomeprazole	20	20	20	20	20	20	20	20	20	20
2	Eudragit RS-100	20	15	---	---	20	30	15	---	---	---
3	Eudragit RL-100	---	15	20	40	---	---	20	30	15	20
4	Eudragit RLPO	---	---	---	---	---	---	---	---	20	15
5	Talc	3	3	3	3	3	3	3	3	3	3
6	Magnesium stearate	3	3	3	3	3	3	3	3	3	3
7	Di.Calcium Phosphate	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s
	Total Weight	100	100	100	100	100	100	100	100	100	100

Evaluation of post compression parameters for prepared Tablets

The designed formulation compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.[49-54]

Weight variation test

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Table No: 6 Pharmacopoeial specifications for tablet weight variation

Average weight of	Average weight of	Maximum percentage
tablet (mg) (I.P)	tablet (mg) (U.S.P)	difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability test

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche friabilator (Lab India, FT 1020). It is expressed in percentage (%). Ten tablets were initially weighed [W (initial)] and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions.

Determination of drug content

The compression tablets of were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Esomeprazole were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In-vitro* dissolution studies**

The *in-vitro* dissolution was carried out using USP type II dissolution apparatus was determined using USP Dissolution testing apparatus type-II (Paddle method; Lab India DS 8000+), Temperature is 37±0.5ºC and RPM is 50. Dissolution medium was maintained at acid buffer (pH-1.2) for 2 hrs, 4.5 pH acetate buffer for 2 hrs, 6.8 pH phosphate buffer for 8 hrs and 7.4 pH phosphate buffer for 12 hrs % Drug release was calculated at various time intervals.[58-65]

The tablets were placed in the dissolution medium and the apparatus was run. At intervals of 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 hours 5 ml aliquots were withdrawn and replacement was done each time with equal amounts of fresh dissolution medium maintained at same temperature. Each 5 ml aliquot was filtered through Whatman filter paper (No.41). 5 ml of sample was diluted to 10 ml acid buffer (pH-1.2) for 2 hrs, 4.5 pH acetate buffer for 2 hrs, 6.8 pH phosphate buffer for 8 hrs and 7.4 pH phosphate buffer for 12 hrs and absorbance of these solutions was measured by using a UV spectrophotometer. Drug concentrations in the sample were determined from standard calibration curve. The release data were calculated.

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics

To study the zero–order release kinetics the release rate data are fitted to the following equation.

$F = Ko\ t$

Where, 'F' is the drug release at time't', and 'Ko' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$Log\ (100-F) = kt$

A plot of log cumulative percent of drug remaining to be released vs.time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$F = k\ t1/2$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer-Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$Mt/ M\infty = K t^n$

Where, Mt/ M∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n=0.5; for zero-order release (case-II transport), n=1; and for super case-II transport, n > 1.In this model, a plot of log (Mt/ M∞) versus log (time) is linear.

Hixson-Crowell release model

$(100-Qt)^{1/3} = 100^{1/3} - KHC.t$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets) [77-81]

Stability Studies

The goal of formulation development is to determine a composition for the final dosage form that results in a safe, efficacious product which remains stable over the course of its intended use.

Under the influence of a variety of environmental factors such as temperature, humidity and light enabling recommended storage conditions, re-test periods and shelf lives.[82-86]

RESULTS AND DISCUSSION

Analytical Method: Graphs of Esomeprazole were taken in Simulated Gastric fluid (pH 1.2) and in pH 6.8 phosphate buffer at 236 nm and 238 nm respectively.

Table 7: Observations for graph of Esomeprazole in 0.1N HCl (236nm)

Concentration (µg/ml)	Absorbance
0	0
5	0.110
10	0.214
15	0.304
20	0.407
25	0.510
30	0.621
35	0.718
40	0.815

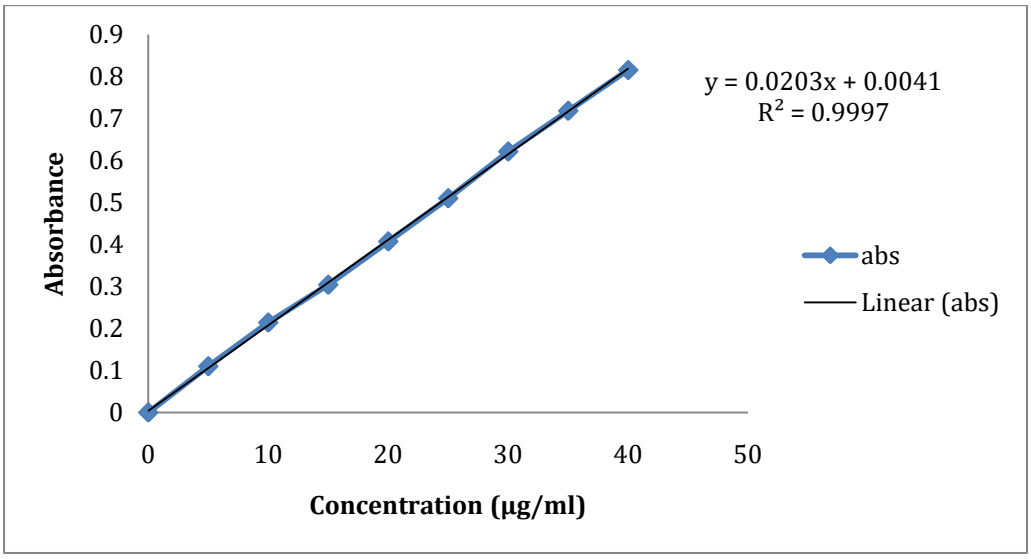

Fig. 2: Standard graph of Esomeprazole in 0.1N HCL

Discussion: Based on above results, it has been inferred that API shows linearity in concentration range of 5-40µg/ml by using Simulated Gastric fluid (pH 1.2). The regression coefficient of calibration curve was found to be 0.999.

Table 8: Observations for graph of Esomeprazole in pH 6.8 phosphate buffer (238nm)

Concentration (µg/ml)	Absorbance
0	0
5	0.093
10	0.199
15	0.291
20	0.384
25	0.487
30	0.589
35	0.698
40	0.795

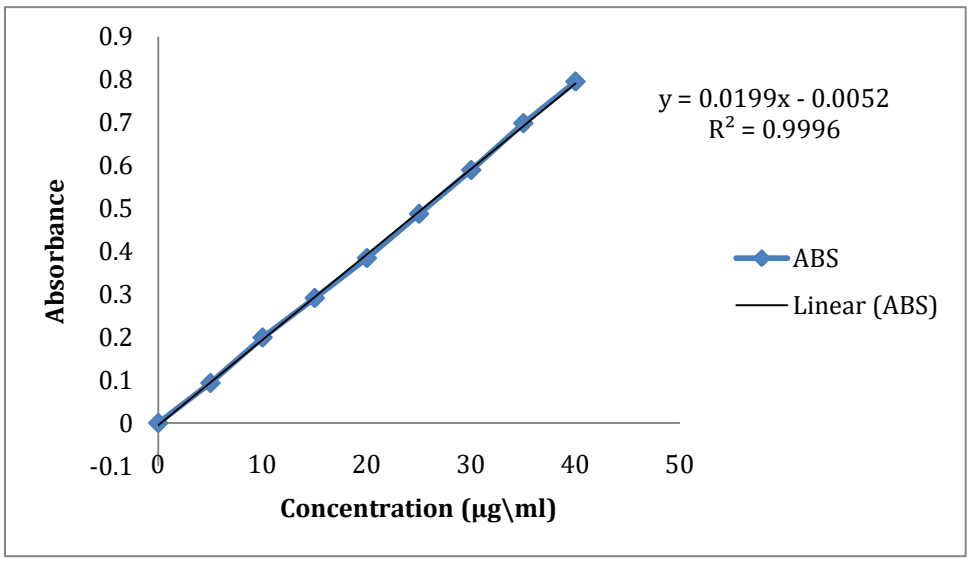

Fig. 3: Standard graph of Esomeprazole in pH 6.8 phosphate buffer

Discussion: Based on above results, it has been inferred that API shows linearity in concentration range of 5-40µg/ml by using pH 6.8 phosphate buffer. The regression coefficient of calibration curve was found to be 0.999.

Drug - Excipient Compatability Studies

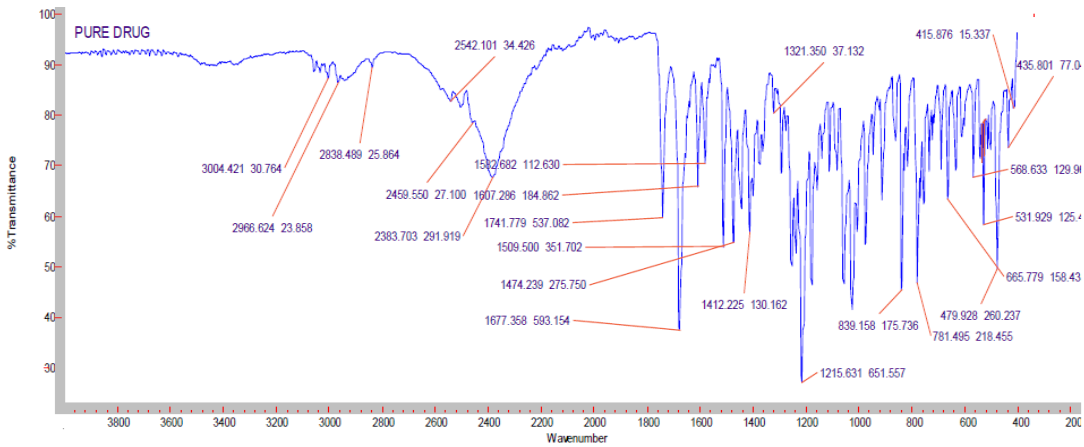

Fig 4: FTIR spectrum of Esomeprazole pure drug

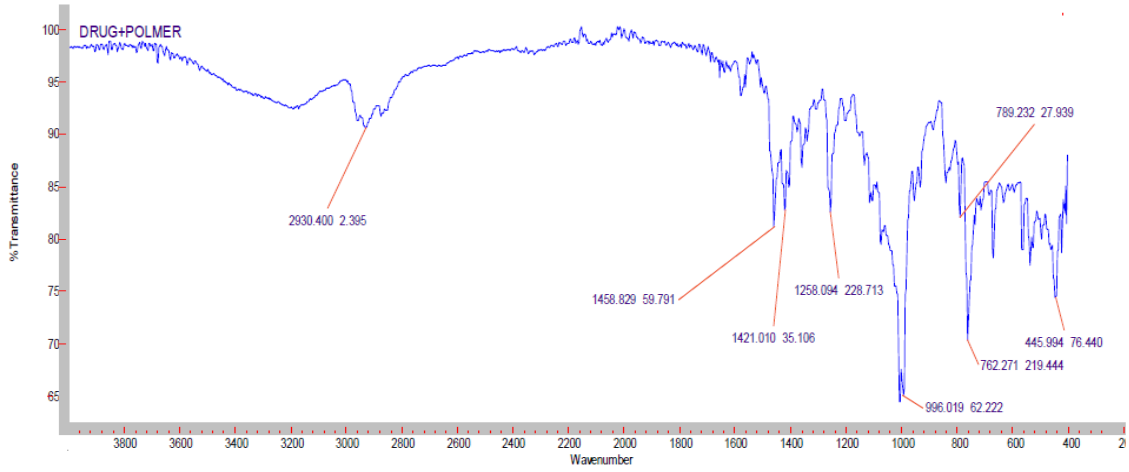

Fig 5: FTIR spectrum of Esomeprazole+Eudragit RSPO

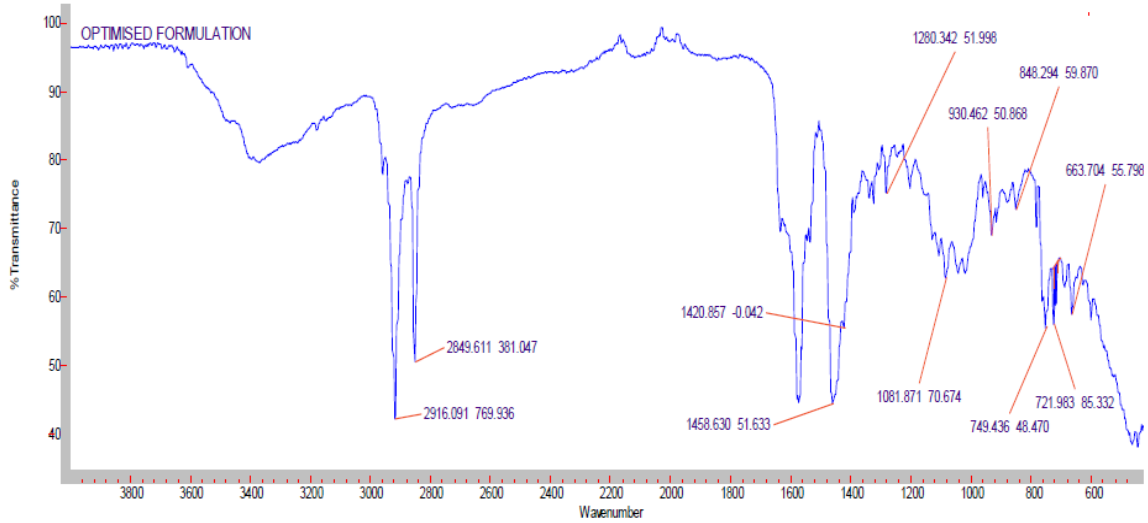

Fig 6: FTIR spectrum of Esomeprazole optimized formulation

Table 9: FT-IR Data Interpretation for Esomeprazole

S. No	Wave number in formulation (cm-1)			Characteristic Wave number range (cm-1)	Bond nature and bond attributed
	Esomeprazole	Esomeprazole + Eudragit RSPO	Optimized formulation		
1.	2966.624	2930.400	2916.091	3400-2400	O-H stretching Carboxylic acid
2.	1509.500	1458.829	1458.630	1600-1475	-C=C- stretching aromatic
3.	1474.239	1458.829	1420.857	1500-1400	C-C stretching ring aromatics
4.	1215.631	1258.094	1280.342	1350-1000	C-N stretching amines
5.	781.495	762.271	749.436	910-665	N-H 10,20 amines
6.	839.158	789.232	848.294	900-690	C-H out-of- plane bend aromatics

Discussion

The progress of a successful formulation depends only on suitable selection of excipients. Hence the physical state of the drug, Esomeprazole Pure drug, Esomeprazole + Eudragit RSPO, Esomeprazole and altered polymers

for occurrence Eudragit RSPO, Talc, Mg.Stearate, Di.Calcium Phosphate individually and the admixture of Esomeprazole and polymers used were studied by FTIR to know the drug - polymer compatibility after interpretation and the results were shown in IR spectra in Fig.:4, 5, 6 and Table.9.

The physicochemical compatibility of the drug and the polymer was established through FTIR studies. IR spectral analysis of Esomeprazole pure drug showed the peaks at wave numbers of 2966.624 (O-H stretching Carboxylic acid), 1509.500 (-C=C-stretching aromatic), 1474.239 (C-C stretch in ring aromatics), 1215.631 (C-N stretch amines), 781.495 (N-H 10, 20 amines), 839.158 (C-H out-of-plane bend aromatics) Confirming the purity of drug with standard respectively.

IR spectral analysis of Esomeprazole+ Eudragit RSPO showed the peaks at wave numbers of 2930.400 (O-H stretching Carboxylic acid), 1458.829 (-C=C- stretching aromatic), 1458.829 (C-C stretch in ring aromatics), 1258.094 (C-N stretch amines), 762.271 (N-H 10, 20 amines), 789.232 (C-H out-of-plane bend aromatics) Confirming the purity of drug with standard respectively.

In the physical mixture of Esomeprazole with various excipients such as Eudragit RSPO, Talc, Mg.Stearate, Di.Calcium Phosphate the major peaks at wave numbers of 2916.091 (O-H stretching Carboxylic acid), 1458.630 (-C=C- stretching aromatic), 1420.857 (C-C stretch in ring aromatics), 1280.342 (C-N stretch amines), 749.436 (N-H 10, 20 amines), 848.294 (C-H out-of-plane bend aromatics). However, extra peaks were absorbed in considerable mixtures which can be due to occurrence of polymers and indicated that there was no chemical interaction between Esomeprazole with various other polymers.

Differential Scanning Calorimetry (DSC)

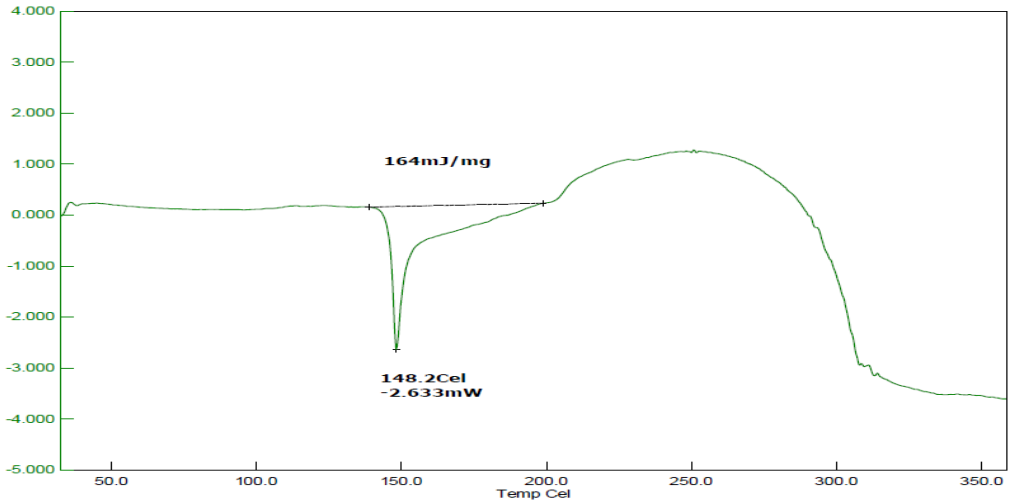

Fig 7: Differential Scanning Calorimetry of Esomeprazole

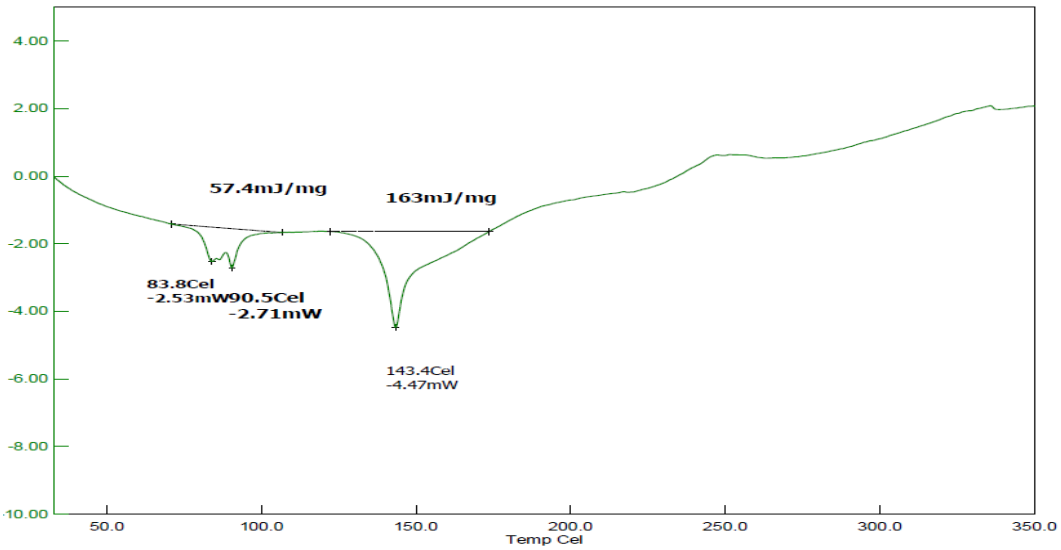

Fig 8: Differential Scanning Calorimetry of Esomeprazole+Eudragit-RSPO

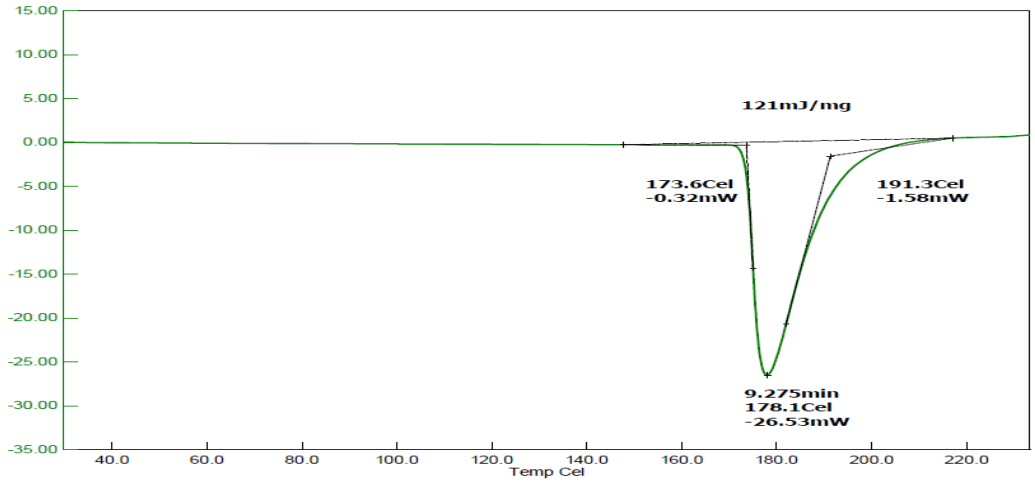

Fig 9: Differential Scanning Calorimetry of Esomeprazole optimized formulation

Table 10: Data of DSC thermogram parameters for Esomeprazole

S. No	Name of ingredients and physical mixtures used in formulation	Temperature at which peak obtained
1.	Esomeprazole	148.2^{0}c
2.	Esomeprazole + Eudragit RSPO	143.4^{0}c
3.	Esomeprazole + Eudragit RSPO + Talc + Mg.Stearate + Di.Calcium Phosphate	178.1^{0}c

Discussion: The compatibility and interactions between drugs and polymer were checked using DSC results obtained were shown in Fig.: 7, 8, 9 and Table. 5.4. The DSC thermograph for Esomeprazole showed melting peak at 148.2°C and the mixer of the Esomeprazole + Eudragit RSPO showed melting points starting at 83.8°C ending at 143.4°C and Esomeprazole + Eudragit RSPO + Talc + Mg.Stearate + Di.Calcium Phosphate showed melting points starting at 173.6°C ending at 178.1°C respectively. The endothermic energy of Esomeprazole was - 2.633 mW and the mixer of the Esomeprazole + Eudragit RSPO and Esomeprazole + Eudragit RSPO + Talc + Mg.Stearate + Di.Calcium Phosphate were -4.47 mW and -26.53 mW respectively. DSC studies were carried out to conclude the compatibility among Esomeprazole and polymers in optimized formulation. From the studies it was manifest that there were no major change in the melting point of Esomeprazole alone and its melting point when it was combined with other polymers of optimized formulation.

FORMULATION STUDIES

***In-vitro* evaluation of Esomeprazole Controlled Release tablets for physico chemical characteristics: (Mean +SD) (n=3)**

Table 11: Flow properties of powder blend for Esomeprazole

Formulation Code	Bulk density (gm/cm3)*	Tapped density (gm/cm3)*	Hausner ratio (HR)*	Carr's index (CI)*	Angle of repose (θ)*
F1	0.51±0.02	0.53±0.03	0.98±0.05	15.96±0.08	24°.13'±0.64
F2	0.50±0.03	0.54±0.06	1.03±0.06	16.18±0.04	23°.36'±0.36
F3	0.49±0.09	0.57±0.04	1.08±0.09	14.68±0.07	24°.69'±0.62
F4	0.52±0.07	0.53±0.06	1.01±0.03	16.59±0.09	25°.26'±0.71
F5	0.53±0.07	0.58±0.05	1.1±0.07	15.84±0.06	24°.98'±0.58
F6	0.54±0.02	0.55±0.08	1.10±0.08	14.98±0.02	24°.12'±0.54
F7	0.55±0.08	0.58±0.03	0.94±0.06	15.98±0.04	23°.86'±0.87
F8	0.56±0.02	0.63±0.04	1.14±0.08	14.84±0.03	25°.02'±0.22
F9	0.54±0.03	0.53±0.04	1.09±0.03	16.98±0.08	24°.98'±0.35

F10	0.49±0.01	0.53±0.09	0.98±0.07	13.98±0.03	25°.64'±0.63
F11	0.48±0.07	0.52±0.05	1.11±0.04	14.54±0.06	27°.79'±0.79
F12	0.50±0.02	0.54±0.03	1.12±0.06	15.34±0.03	26°.98'±0.25
F13	0.49±0.03	0.61±0.07	1.1±0.05	13.52±0.02	24°.63'±0.11
F14	0.47±0.08	0.57±0.02	0.99±0.03	12.34±0.05	26°.35'±0.73
F15	0.51±0.07	0.59±0.04	1.12±0.07	14.63±0.02	27°.19'±0.59
F16	0.50±0.05	0.56±0.06	1.14±0.06	11.14±0.05	25°.23'±0.34
F17	0.49±0.01	0.59±0.09	1.12±0.08	12.34±0.03	26°.55'±0.27
F18	0.50±0.06	0.58±0.04	1.11±0.06	13.43±0.06	24°.99'±0.13
F19	0.49±0.03	0.55±0.07	0.99±0.02	12.39±0.01	25°.45'±0.45

Discussion: Tablet powder blend was subjected to various preformulation parameters. The bulk density of all the formulations was found to be in the range of 0.48±0.07 to 0.56±0.02 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.52±0.05 to 0.63±0.04 showing the powder has good flow properties. The hausner's ratio ranging between 0.94±0.06 to 1.14±0.08 indicating the powder has good flow properties. The Carr's index of all the formulations was found to be in the range of 11.14±0.05 to 16.98±0.08. The angle of repose of all the formulations was found to be in the range of 23°.36'±0.36 to 27°.79'±0.79. All these value indicates that the powder blend has good flow properties.

***In-vitro* evaluation of Esomeprazole Controlled Release tablets for Post Compression characteristics:**

Table 12: Physico Chemical Characterization of Esomeprazole Controlled Release Tablets

Formulation Code	Weight variation (mg)	Hardness (kg/cm2)	Friability (%)	Thickness (mm)	Drug content (%)
F1	100±0.48	4.5±0.41	0.50±0.13	3.8±0.29	99.17±0.73
F2	101.4±0.86	4.1±0.23	0.59±0.48	4.1±0.24	98.96±0.36
F3	99.1±0.86	3.9±0.16	0.61±0.29	3.4±0.14	99.74±0.64
F4	101.6±0.86	3.5±0.39	0.75±0.66	4.9±0.57	98.96±0.11
F5	98.9±0.11	4.2±0.22	0.56±0.25	3.9±0.35	99.59±0.35
F6	99.8±0.32	4.4±0.56	0.65±0.18	4.1±0.23	99.87±0.13
F7	98.4±0.53	3.8±0.12	0.59±0.74	3.4±0.24	98.85±0.37
F8	101.3±0.42	3.3±0.11	0.49±0.33	3.3±0.61	99.36±0.31
F9	99.1±0.44	3.8±0.37	0.57±0.37	3.5±0.27	99.61±0.44
F10	101±0.52	3.7±0.25	0.64±0.42	3.9±0.65	98.67±0.76
F11	99.2±0.43	4.2±0.62	0.59±0.52	4.2±0.45	99.56±0.52
F12	99.5±0.72	3.9±0.53	0.67±0.76	3.8±0.17	98.59±0.25
F13	101.2±0.21	3.7±0.18	0.64±0.17	4.7±0.89	99.62±0.29
F14	98.8±0.82	4.1±0.52	0.59±0.44	3.6±0.42	99.42±0.27
F15	101.2±0.23	3.9±0.47	0.66±0.52	4.2±0.59	98.95±0.26
F16	99.1±0.71	4.2±0.24	0.65±0.46	3.7±0.62	99.46±0.52
F17	101.5±0.65	3.8±0.43	0.56±0.52	3.8±0.55	99.59±0.56
F18	99.5±0.65	3.9±0.53	0.59±0.19	3.7±0.74	99.68±0.96
F19	100.3±0.89	4.1±0.71	0.57±0.34	3.9±0.28	98.97±0.35

Discussion

Appearance

The tablets were observed visually and did not show any defect such as capping, chipping and lamination.

Physical characteristics

The physical characteristic of Esomeprazole Controlled release tablets (F1 to F19) such as weight variation, hardness, friability, thickness, and drug content were determined and results of the

formulations (F1 to F19) found to be within the limits specified in official books.

Weight Variation

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet. Average weight of the tablet is approximately in range of 98.4±0.53 to 101.6±0.86, so the permissible limit is ±7.5% (more than 80mg Less than 250mg). The tablet weights were within the Pharmacopoeial specifications.

Tablet Hardness

Hardness of the three tablets of each batch was checked by using Monsanto hardness tester. The results showed that the hardness of tablets was found to be in the range of 3.3±0.11 to 4.5±0.41kg/cm2. This indicates good tablet strength.

Percent Friability

Percentage friability of all the formulations was found to be in between 0.49±0.33 to 0.75±0.66%. This indicated good handling property of the prepared CR tablet.

Dimension (Diameter and Thickness)

Thickness and diameter specifications may be set on an individual product basis. Excessive variation in the tablet thickness and diameter can result in problems with packaging as well as consumer acceptance. The size (diameter) of the tablets of all formulations were found to be 6.0±0.0 mm and thickness ranged between 3.3±0.61 to 4.9±0.57.

Drug content

The content of active ingredients in the formulation was found to be between 98.59±0.25 to 99.74±0.64 % w/w, which is within the specified limit as per IP (i.e. 90-110% w/w).

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In-Vitro* Dissolution Studies of Esomeprazole Controlled Release Tablets**

Table 13: *In-Vitro* drug release studies of Esomeprazole Controlled Release tablets (F1-F7)

Time (hours)	Cumulative % Drug Release						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
1	6.98±0.74	6.42±0.59	7.08±0.45	7.35±0.76	15.55±0.35	6.42±0.64	14.21±0.69
2	7.86±0.36	8.52±0.65	18.73±0.87	14.39±0.57	19.94±0.47	12.59±0.43	19.65±0.76
4	14.65±0.83	13.26±0.43	27.74±0.23	19.22±0.46	28.33±0.54	24.26±0.94	24.98±0.97
6	18.64±0.52	22.73±0.93	39.11±0.72	24.21±0.95	35.29±0.72	38.12±0.67	28.76±0.24
8	23.36±0.19	33.79±0.34	47.44±0.37	31.42±0.21	40.11±0.46	49.94±0.43	35.34±0.76
10	29.82±0.23	41.21±0.87	58.35±0.92	39.73±0.36	48.87±0.25	57.15±0.79	44.50±0.53
12	34.61±0.78	50.22±0.54	63.53±0.63	51.29±0.28	55.83±0.92	69.93±0.64	54.56±0.94
14	43.07±0.92	57.33±0.11	69.89±0.56	60.11±0.72	61.12±0.29	75.66±0.92	61.05±0.58
16	48.71±0.45	68.03±0.45	74.29±0.43	72.14±0.93	69.76±0.62	81.78±0.52	64.98±0.86
18	57.22±0.69	74.39±0.37	79.01±0.96	78.77±0.38	73.58±0.91	85.19±0.74	72.03±0.75
20	68.35±0.43	76.15±0.92	81.43±0.53	83.64±0.67	79.56±0.68	91.26±0.59	76.92±0.68
22	77.23±0.34	81.12±0.54	83.36±0.68	86.89±0.46	85.32±0.75	94.18±0.86	85.88±0.93
24	86.77±0.28	88.27±0.45	90.67±0.96	91.03±0.25	91.93±0.54	97.47±0.97	91.12±0.78

Table 14: *In-Vitro* drug release studies of Esomeprazole Controlled Release tablets (F8-F14)

Time (hours)	Cumulative % Drug Release						
	F8	F9	F10	F11	F12	F13	F14
0	0	0	0	0	0	0	0
1	10.53±0.81	10.11±0.67	8.25±0.34	7.52±0.36	7.82±0.46	8.15±0.73	7.63±0.48
2	19.29±0.52	16.74±0.73	11.72±0.73	10.16±0.73	10.26±0.82	10.61±0.62	9.53±0.63
4	29.21±0.98	28.37±0.22	18.53±0.62	16.56±0.51	17.28±0.53	13.72±0.81	16.55±0.41

6	36.36±0.64	33.44±0.87	25.43±0.73	21.62±0.98	24.37±0.69	19.28±0.63	20.36±0.87
8	41.39±0.76	43.45±0.53	33.72±0.83	26.22±0.42	35.28±0.23	24.11±0.92	26.25±0.59
10	49.62±0.52	49.34±0.82	42.13±0.54	34.75±0.61	44.71±0.58	30.79±0.67	31.82±0.98
12	58.01±0.97	58.11±0.98	54.46±0.98	40.17±0.49	53.19±0.82	35.27±0.85	36.29±0.72
14	65.47±0.42	66.94±0.43	63.29±0.46	44.34±0.76	61.67±0.93	46.09±0.98	48.26±0.63
16	73.55±0.55	69.38±0.32	75.67±0.75	49.25±0.21	73.98±0.34	49.27±0.43	48.71±0.42
18	77.48±0.64	74.14±0.82	83.24±0.37	56.71±0.73	80.32±0.86	58.99±0.81	57.22±0.65
20	80.35±0.98	79.76±0.63	87.52±0.83	67.23±0.64	84.41±0.91	66.45±0.79	69.47±0.53
22	84.66±0.33	84.88±0.58	91.79±0.65	78.76±0.82	88.27±0.38	74.32±0.66	78.83±0.66
24	90.87±0.84	89.98±0.97	93.82±0.24	88.29±0.34	92.61±0.65	89.13±0.43	90.77±0.98

Table 15: *In-Vitro* drug release studies of Esomeprazole Controlled Release tablets (F15-F19)

Time (hours)	Cumulative % Drug Release				
	F15	F16	F17	F18	F19
0	0	0	0	0	0
1	9.25±0.53	5.99±0.46	7.78±0.63	7.45±0.41	8.87±0.35
2	15.53±0.41	9.93±0.83	10.72±0.76	9.98±0.76	10.49±0.26
4	20.35±0.74	13.27±0.32	19.81±0.82	15.62±0.59	19.36±0.18
6	22.83±0.92	19.29±0.57	27.79±0.85	19.34±0.22	26.87±0.63
8	29.31±0.46	24.93±0.85	34.65±0.61	25.87±0.27	34.23±0.24
10	38.79±0.67	30.26±0.92	45.87±0.23	30.68±0.43	41.19±0.76
12	49.93±0.82	37.37±0.24	54.46±0.53	36.92±0.12	53.55±0.55
14	58.37±0.53	45.25±0.52	62.76±0.38	44.26±0.26	62.87±0.38
16	70.83±0.54	49.82±0.43	74.16±0.45	49.98±0.55	73.82±0.62
18	79.98±0.45	58.92±0.72	81.34±0.68	58.45±0.87	81.19±0.74
20	84.35±0.34	69.29±0.89	85.11±0.75	69.87±0.55	84.52±0.43
22	88.26±0.78	78.47±0.49	89.67±0.57	78.92±0.64	88.44±0.14
24	92.47±0.33	87.93±0.45	91.43±0.28	89.79±0.74	92.12±0.25

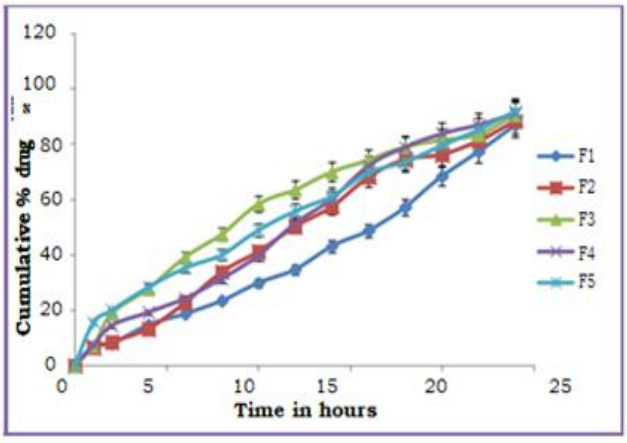

Fig 10: Dissolution graphs for the formulations F1 to F5

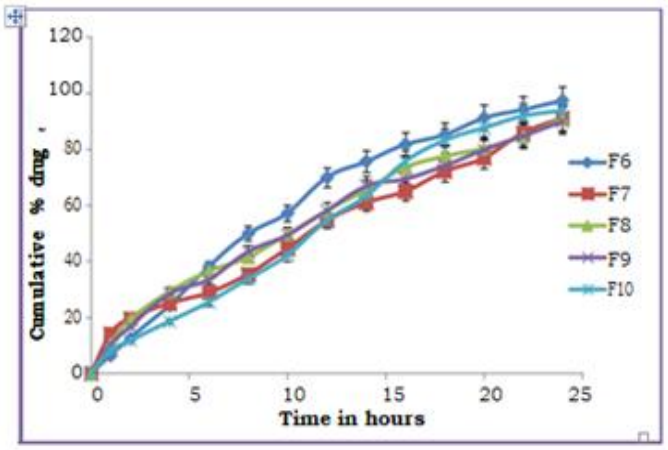

Fig 11: Dissolution graphs for the formulations F6 to F10

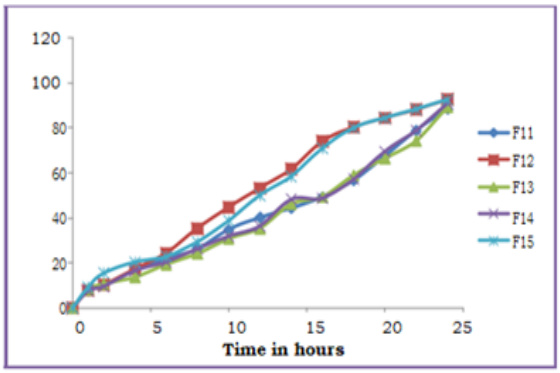

Fig 12: Dissolution graphs for the formulations F11 to F15

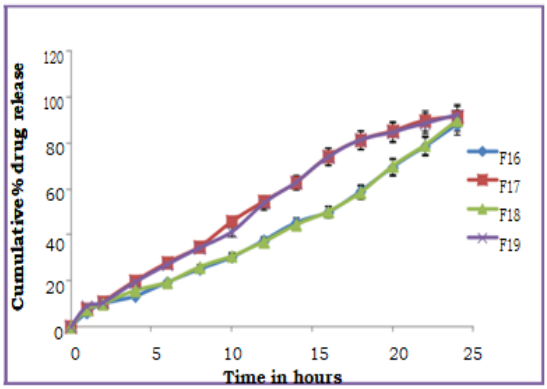

Fig 13: Dissolution graphs for the formulations F16 to F19

Discussion

The prepared Esomeprazole CR tablets were evaluated for the dissolution studies in acid buffer (pH-1.2) for 2 hrs, 4.5 pH acetate buffer for 2 hrs, 6.8 pH phosphate buffer for 8 hrs and 7.4 pH phosphate buffer for 12 hrs % drug release was calculated at various time intervals. The results were shown in the Table.13, 14, 15 and Fig.10, 11, 12, 13.

To prepare the different controlled release formulations of Esomeprazole tabletswith different polymers like Polymethacrylates such as Eudragit-S100, L-100, RSPO, RS-100, RL-100, RLPO and Talc is glidant, magnesium stearate is lubricant and Di.Calcium Phosphate was used as diluents by Direct Compression method.

Formulation F1 and F2 containing Eudragit-S100. The Formulation F1, F2 have shown cumulative % drug release of 86.77±0.28 %, 88.27±0.45 % respectively at the end of 24th hr. Formulation F3 and F4 containing Eudragit-L100. The Formulation F3, F4 have shown drug release of 90.67±0.96 %, 91.03±0.25 % respectively at the end of 24th hr.

Formulation F5 and F6 containing Eudragit-RSPO. The Formulation F5, F6 have shown drug release of 91.93±0.54 %, 97.47±0.97 % respectively at the end of 24th hr. Formulation F7 containing combination of Eudragit-S100 and Eudragit-L100.

The Formulation F7 has shown drug release of 91.12±0.78 % at the end of 24th hr. Formulation F8 containing Eudragit-S100. The Formulation F8 has shown drug release of 90.87±0.84 % at the end of 24th hr. Formulation F9 containing combination of Eudragit-L100 and Eudragit-RSPO. The Formulation F9 has shown drug release of 89.98±0.97 % at the end of 24th hr.

Formulation F10 containing Eudragit-RS100. The Formulation F10 has shown drug release of 93.82±0.24 % at the end of 24th hr. Formulation F11 containing combination of Eudragit-RS100 and Eudragit-RL100. The Formulation F11 has shown drug release of 88.29±0.34 % at the end of 24th hr. Formulation F12 and F13 containing Eudragit-RL100. The Formulation F12, F13 has shown drug release of 92.61±0.65 %, 89.13±0.43 % respectively at the end of 24th hr.

Formulation F14 and F15 containing Eudragit-RS100. The Formulation F14, F15 has shown drug release of 90.77±0.98 %, 92.47±0.33 % respectively at the end of 24th hr. Formulation F16 containing combination of Eudragit-RS100 and Eudragit-RL100. The Formulation F16 has shown drug release of 87.93±0.45 % at the end of 24th hr. Formulation F17 containing Eudragit-RL100. The Formulation F17 has shown drug release of 91.43±0.28 % at the end of 24th hr.

Formulation F18 and F19 containing combination of Eudragit-RL100 and Eudragit-RLPO. The Formulation F18, F19 has shown drug release of 89.79±0.74 %, 92.12±0.25 % respectively at the end of 24th hr.

The results of drug release shown that the Esomeprazole was released in a controlled behaviour from all the formulations where formulation F-6 showed maximum cumulative % drug release i.e. 97.47±0.97 at the end of 24th hour which was the intent of the finalized formulation while others being not reached to the time point of maximum release still extending the release.

Comparison of *In-Vitro* Drug release studies of Optimized Esomeprazole CR Formulation (F-6) with Innovator Product:

Table 16: Comparative *In-vitro* drug release studies of optimized formulation of Esomeprazole (F-6) with Innovator product

Time (Mins)	F-6	Innovator Product
0	0	0
10	---	38.25±0.78
20	---	59.77±0.24
30	---	76.86±0.18
45	---	97.12±0.24
60	6.42±0.64	---

120	12.59±0.43	---
220	24.26±0.94	---
340	38.12±0.67	---
460	49.94±0.43	---
580	57.15±0.79	---
700	69.93±0.64	---
820	75.66±0.92	---
940	81.78±0.52	---
1060	85.19±0.74	---
1180	91.26±0.59	---
1300	94.18±0.86	---
1420	97.47±0.97	---

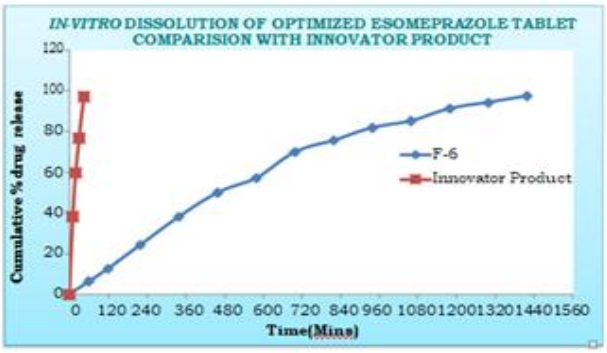

Fig. 14: Comparison of *In-Vitro* Drug release Studies of Optimized Formulation of Esomeprazole (F-6) with Innovator Product

Discussion:

Esomeprazole is available as conventional immediate release tablet dosage form as in the brand name of Nexium 20mg Tablets.

In the present research work Esomeprazole Controlled Release Tablets 20mg was formulated and the composition was optimized with an objective of prolonging the drug release capable of 24 hrs and the *in-vitro* drug release of optimized Esomeprazole Controlled Release Tablets 20mg was evaluated and was compared against the *in-vitro* drug release of corresponding Innovator product.

The drug release from Nexium 20mg tablets was about 97.12±0.24 cumulative % drug release in 45 minutes, whereas finalized Controlled release tablet dosage containing Drug to Polymer (Esomeprazole:Eudragit-RSPO) at 1:2 ratios (F-6) has shown the cumulative % drug release of 97.47±0.97 at the end of 24 hours. The formulation which has shown the drug release at Zero order / constantly for the preferred time period of time was deliberate as optimized formulation.

Based on *in-vitro* release studies, it was clearly evident that the drug release from finalized Controlled release tablet dosage form has been prolonged for 24 hours, whereas marketed Innovator product has shown almost complete drug release in 45 minutes. Based on the results, it can be concluded that the innovator product needs to be administered 2 to 3 times in a day, while the Esomeprazole Controlled release tablet can be administered once daily is sufficient to continue the therapeutic concentration.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table 17: Esomeprazole Release Kinetic Parameters for Optimized Formulation

Formulation code	Zero Order	First Order	Higuchi	Best fit	Korsmeyer-Peppas		Release Mechanism
	R^2	R^2	R^2		R^2	n-value	
F6	0.992	0.984	0.969	Zero Order	0.991	0.951	Non-Fickian (or) Anomalous Diffusion

Optimized formulation (F-6) for release kinetics graphs:

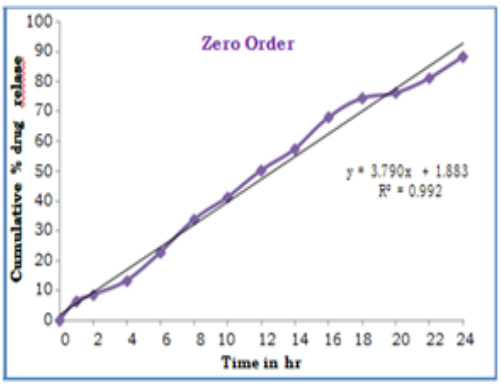

Fig. 15: Zero order release kinetics of Esomeprazole Optimized Formulation (F-6)

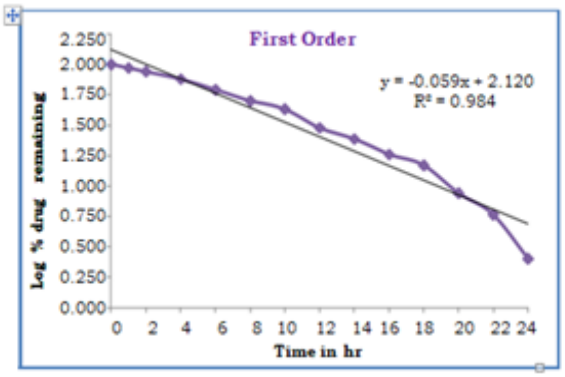

Fig. 16: First order release kinetics of Esomeprazole Optimized Formulation (F-6)

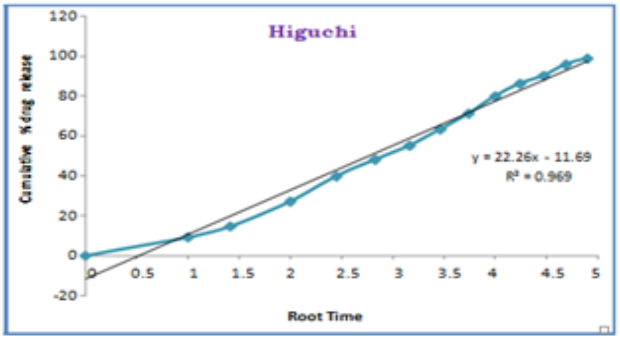

Fig. 17: Higuchi order release kinetics of Esomeprazole Optimized Formulation (F-6)

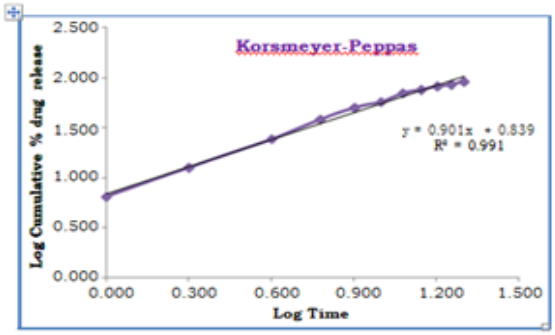

Fig. 18: Korsmeyer-Peppas order release kinetics of Esomeprazole Optimized Formulation (F-6)

Kinetics of *In-vitro* Dissolution for Optimized Formulation:

In-vitro dissolution kinetic parameter from optimized formulation of Esomeprazole controlled release tablet was calculated and the reports are given in table.17 and Fig.15, 16, 17, 18. It was examined the drug release kinetic from the formulation was followed zero order as the R2 value of zero order was establish to be 0.992 and the mechanism of drug release was found to be following Non-Fickian (or) Anomalous Diffusion as the n value of korsemeyer-peppas was found to be 0.951.

Stability Studies of Esomeprazole Optimized Formulation:

Accelerated Stability studies of optimized formulation were performed for a period of 6 months as per ICH guidelines. The reports of various evaluation parameters such as Weight variation, Thickness, hardness, friability, Drug content, *In-vitro* dissolution at 24th hour of Esomeprazole at various predetermined time intervals. The results are obtained in table. 5.12. No major segregation was initiate between evaluated parameters before and after storage and all are in acceptable limits. The tablets showed satisfactory at Accelerated temperature 400C ± 20C / 75% RH ± 5%.

Stability studies of Esomeprazole optimized formulation (F-6):

After storage the formulation was analyzed for various physical parameters, results are showed in Table 18.

Table 18: Stability study of Optimized formulation (F-6) of Controlled release Esomeprazole tablets at Accelerated temperature 40⁰ C ± 2⁰ C / 75% RH ± 5%.

Parameter	Initial	Accelerated temperature (40⁰ C ± 2⁰ C / 75% RH ± 5 %)			
		1st Month	2nd Month	3rd Month	6th Month
Weight variation (mg)	99.8± 0.32	99.1± 0.43	98.9± 0.21	99.2± 0.48	99.5± 0.27
Thickness (mm)	4.1±0.23	4.1±0.25	3.9±0.97	4.1±0.42	4.1±0.74
Hardness(kg/cm2)	4.4±0.56	4.3±0.85	4.2±0.73	4.3±0.65	4.4±0.31
Friability (%)	0.65±0.18	0.64±0.73	0.64±0.31	0.64±0.42	0.65±0.54
Drug content (%/tablet)	99.87±0.13	99.49±0.84	98.63±0.61	99.55±0.32	99.41±0.64
In-vitro drug release at 24th hour	99.47±0.97	99.35±0.84	98.61±0.36	99.73±0.11	99.23±0.52

The current research work envisaged was an attempt to development of controlled release formulations of Esomeprazole to improve bioavailability. Esomeprazole is a proton pump inhibitor used to treat gastroesophageal reflux disease (GERD). It is a short biologicalhalf-life (1to1.5 hrs), poor bioavailability (50 to 68%) and narrow therapeutic index. since of all these parameters esomeprazole was chosen as a good candidate for controlled drug delivery systems.

- ✓ Preformulation studies were performing for Esomeprazole to recognize the Drug excipients interactions using FTIR and DSC studies, showed that excipient were compatible.
- ✓ Esomeprazole controlled release tablets were formulated by direct compression method by distinct Polymethacrylates such as Eudragit-S100, Eudragit -L100, Eudragit-RSPO, Eudragit-RS100, Eudragit-RL100, Eudragit-RLPO.

- ✓ To prepare the different controlled release formulations of Esomeprazole tablets with different polymers like Polymethacrylates such as Eudragit-S100, L-100, RSPO, RS-100, RL-100, RLPO and Talc is glidant, magnesium stearate is lubricant and Di. Calcium Phosphate was used as diluents by Direct Compression method.
- ✓ Esomeprazole formulated tablet blend and tablets were subjected to their pre and post formulation characteristics likeflow properties and weight variation, hardness, friability, drug content. Results of all these parameters were within the pharmacopoeial limits.
- ✓ Developed formulations are deliberate for *in-vitro* dissolution and release kinetic studies. Based on the results F-6 formulation was chosen as a superlative among all the formulations in the point of drug release and mechanism. This formulation was kept for stability study for period of 6 months according to the ICH guidelines, results were conformed the optimized one is stable.

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